SPECIAL SESSION
ADVANCING AQUACULTURE DRUG APPROVALS BY
STRATEGIC COORDINATED RESEARCH

2ND MEETING OF THE
NATIONAL AQUACULTURE DRUG RESEARCH FORUM
August 04, 2005

Held in conjunction with the 11th Annual Drug Approval Coordination Workshop

**MISSION STATEMENT**

"To advance scientific knowledge and coordinate research activities
to expedite the approval of new animal drugs."

The goal of the forum is to develop a strategic plan component to work on issues relative to drugal approval research activities, including (1) providing a forum for the exchange of information and mutual education between CVM review teams and representatives from academia, the pharmaceutical industry, aquaculture industry, and other government agencies, and (2) to create a mechanism to broadly disseminate information relative to drug approval research activities.

Propose Shared Leadership:

| | |
|---|---|
| FDA-OR | Renate Reimschuessel |
| USGS | Mark Gaikowski |
| USFWS | Jim Bowker |
| USDA-ARS | Dave Straus |

Effective group structure includes the following:

- Group must be sustainable
- Group must have direction
- Those responsible must be accountable
- Group must establish monitoring program to evaluate progress
- Group must effectively and efficiently complete tasks

## TECHNICAL PROJECT TEAMS

### ENVIRONMENTAL RISK ASSESSMENT

Co-leaders: Charles Eirkson & Mark Gaikowski

### TARGET ANIMAL SAFETY & EFFICACY

Co-leaders: Jim Bowker & Don Prater

### ANALYTICAL METHODS VALIDATION

Co-leaders: Jeff Meinertz & James Nitao

### ANTIMICROBIAL RESISTANCE

Co-leaders: Christine Moffitt & Steve Yan

### EDUCATION AND OUTREACH

Co-leaders: Gary Jensen and Susan Storey
Participants: Tom Bell & Roy Yanong

### ROLES AND RESPONSIBILITIES OF NARDF CO-CHAIRS AND

**TECHNICAL PROJECT TEAM CO-LEADERS AND MEMBERS:**

**CO-CHAIRS:**

1. Overall coordination to accomplish NADRF mission and objectives
2. Serve as liaison to members of respective Federal Agency's (USFDA-CVM, USFWS, USGS, and USDA)
3. Arrange teleconferences and meetings
4. Disseminate information, minutes, or notes from scheduled NADRF meetings to Co-Leaders and Members
5. Coordinate and communicate progress reports from Technical Project Team Leaders
6. Report to JSA WGQAAP on progress and accomplishments
7. Evaluate progress toward goals and prioritize efforts
8. Review and comment on documents and reports as requested
9. Arrange for Peer Review of team final products
10. Establish and maintain an avenue to broadly disseminate related information
11. Assist in activities as needed

**TECHNICAL PROJECT TEAM CO-LEADERS:**

1. Coordinate and direct Project Team activities, communications, and reporting
2. Monitor progress and accomplishments
3. Communicate any needs or constraints to Co-Chairs
4. Arrange for Project Team teleconferences and meetings
5. Evaluate progress toward Project Team goals and prioritize efforts
6. Update Co-Chairs with Project Team activities and accomplishments
7. Develop, review, and comment on documents and reports
8. When able, attend/participate in NARDF meetings or teleconferences
9. Recruit other members as needed to ensure Team progress is maintained
10. Assist in activities as needed

**TECHNICAL PROJECT TEAM MEMEBERS:**

1. Assist determining Project Team goals and prioritized work activities
2. Gather, analyze, and review information and data
3. Disseminate information via reports, manuscripts, presentation, or on a dedicated web site
4. Assist Project Team Co-Leaders as needed
5. Report progress, needs, or constraints to Co-Leaders
6. Attend meetings and/or participate in teleconferences as requested
7. Assist recruiting other members as needed

One of the goals for the August 04 meeting was to provide break-out sessions for Technical Project Team Co-Leaders and Members to further discuss and develop an action plan to

address one or more high priority issues. Below is a synopsis of those discussions and actions plans:

**TARGET ANIMAL SAFETY & EFFICACY**

Co-leaders: Don Prater & Jim Bowker

Participants: Mark Gaikowski, Gary Jensen, Pat Gaunt, Jim Preacher, Dave Straus, Susan Storey, Anita Kelly, Tom Goodrich, Jeff Hill, Roy Yanong, Jennifer Matysczak, Alan Johnson, Dan Carty, Molly Bowman, & Miranda Dotson

The group had previously decided to try to address one issue that might be readily achievable and one issue in which considerable effort will be required to adequately address. At this meeting, it was decided that addressing how to deal with concomitant diseases during field efficacy trials would be the issue that we hope can be addressed in a relatively short period of time, and establishing disease models to minimize the number of pivotal field efficacy trials required to support a specific disease claim. It is anticipated that the disease model issue will require substantial time and effort to complete.

**DISEASE MODELS**

There is a widely-recognized need to develop a science-based argument for the use of disease models to reduce the number of field trials required for completion of an efficacy technical section for a specific disease claim for a specific fish or category of fish (i.e., cold, cool, or warmwater fishes). Scientific rationale is needed to justify why a study cannot be done in the field. Rational such as management issues or insufficient time or resources are not valid. Appropriate rationale must be propose during a pre-submission meeting with the sponsor and CVM.

Disease models need to be validated, need to be consistent, and need to work at multiple facilities under various environmental conditions. A proposal (with supportive evidence) for inducing a disease, including methods used, must be acceptable to CVM. The level of morbidity and mortality resulting from such a model must replicate levels observed in natural outbreaks of disease. In addition, culture conditions must be as close to field conditions as possible.

When testing facility uses a re-use system, measures must to taken to ensure water from test units does not contain drugs or chemicals that may have been used on other areas of the rest facility.

There is currently no CVM guidance for disease models, but any licensed vaccine would have required a validated disease model, CVB may have model guidance. Also, Freedom of Information Summaries for the poultry industry may be a source of disease model.

Action Plan

1. Contact CVB for a guidance document for development of vaccines.
2. Discuss with CVM whether CVB guidance documents will be sufficient.
3. Draft scientific argument to justify using disease models.
4. Determine disease model validation method.
5. Determine most appropriate mode of infection to most closely mimic a natural infection.
6. Draft a Rationale Template

Template for Rationale

1. Label Claim
   - State the label claim and focus on it
   - Propose a combination of studies to complete it
2. Disease
   1. What is the pathogenesis of the disease?
   2. The etiological agent?
   3. Any intermediaries?
3. Primary Variable
   - What is the primary variable
   - Why it cannot be reached in the field
4. Inferential Value
   - Must support this
5. Etiological Agent
   - Must be derived from field isolate
   - Describe why isolate it representative of pathogen
   - Number of infectious units required to elicit disease response
   - Determine range of mortality associated with standard disease model infection.
   - Determine if there is a need to test multiple isolates?
6. Stressors
   - Must occur within pathogenesis of disease
   - Cannot be injected corticoid immune suppressor
   - Abrasions, temperature shock, etc. may be acceptable to CVM - propose to CVM
   - Describe why you chose a particular stress and how it fits with the disease and species.
7. Culture and Rearing Conditions
8. Dose Characterization
   - Range finding study to determine dose
   - Not typically as precise as dose confirmation, can be results from pilot tests
9. Dose Confirmation
   - Study to test dose(s) against control
   - Needs to be similar to field studies
10. Independent Substantiation
    - Will model work in another location in someone else's hands?
    - At least 3 locations and 2 investigators

Develop a disease model: Mark Gaikowski will attempt first draft of disease model outline

Others involved in project:

| | |
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| University - Pat Gaunt | USGS/ARS - Dave Straus |
| Industry - Vaughn Ostland? | USFWS - Joy Evered? |
| CVM - Don Prater | USFWS - Molly Bowman |

**CONCOMITANT DISEASES**

Concomitant pathogens can compromise the outcome of field efficacy trials. Under what

situations/conditions will such studies by “salvageable?” At what level is the pathogen present, at what level would treatment be recommended, and at what level would morbidity/mortality evident. Is the test article effective against the secondary pathogen?

- Will secondary pathogen affect mortality.
- If secondary pathogen is sensitive to test article - end study or design method to monitor presence and level of secondary pathogen. Describe pathogenesis.
- Find out effect on primary pathogen

Identify when fish would’ve been treated for secondary pathogen at that particular facility. Build accountability into protocol, exclusion section, you can exclude a tank, but document events leading up to this point (disease level, treatment, etc.).

Distinguish a secondary infection from a disease syndrome - what is the concomitant disease. Is this a secondary infection or a re-infection or re-occurrence of the same disease outbreak? What is important to consider when conducting field trials.

Point to Consider Document

1. Definition of a concomitant disease;
2. What is important to consider when conducting field efficacy trials
3. Prospectively
   - What you can add to the protocol (if we see this, we will do this)
4. Additional Data
   - What you should do during the study
5. Retrospectively
   - What you should put into the final study report

Develop A Points to Consider document: Jim Bowker, Pat Gaunt, and Susan Storey

**ENVIRONMENTAL RISK ASSESSMENT**

Co-leaders: Mark Gaikowski & Chuck Erickson
Participants: Eric Silberhorn (CVM), Mike Mason (Iowa DNR), Paul Curtis (Hubbs SeaWorld), Bonnie Johnson (USFWS, AADAP), Larry Schmidt (USGS, UMESC), and Jan Holland (ANZL)

The first part of the meeting covered the objective from the last meeting. Chuck Eirkson reported that a key word list to search for environmental information had been developed and circulated to participants of the first meeting. A list of priority drugs had been developed by Roz Schnick and could be used for searching data bases for environmental parameters.

Data on several priority drugs such as oxytetracycline, hydrogen peroxide and chloramine-t was being actively collected and included in environmental assessments by Larry Schmidt and Mark Gaikowski. These documents were under active review and revision by FDA and USGS.

Discussion then shifted to future needs and research.

1. It was agreed that it would be good to develop a roadmap or question and answer document that would assist in the development of formal Environmental Assessments for FDA review. This would assist with data collection, identification of data gaps and research needs for specific

aquaculture drug products.

Objective: Develop guidance for developing Environmental Assessments.

2. It was recognized that the group was primarily focused on freshwater systems but it was recognized that salt water aquaculture was being actively developed. It was expressed that there is a need to specifically address marine systems in the environmental review and possibly for the research forum as a whole. Members for marine systems need to be identified.

Objective: Consider whether marine systems should be included in the next meeting of Annual Drug Approval Coordination Workshop

Objective: Identify individuals in marine aquaculture systems who can contribute to the environmental review of new animal drugs for marine aquaculture.

3. Chuck Eirkson and Eric Silberhorn reported that they were continuing the development of methods for calculating predicted environmental concentration (PEC) or environmental introduction concentration (EIC) for the use aquaculture drugs in various systems (flow-through, pond, intensive). The methods would be used in the environmental assessments to compare with available toxicity data to determine whether there is potential for environmental impacts. If impacts are possible, then limitation on the introduction on aquaculture drugs into surface water will be needed. They have been meeting with EPA, Office of Water, and have tentatively agreed that if limitations are needed for flow through systems, water quality criteria following EPA methods would be used.

Mark Gaikowski reported that he is continuing to develop data to model drug effluents from flow-through hatcheries. This data can provide a basis for the standard PEC method for flow-through systems.

Additional work needs to be started for ponds and intensive systems. Paul Curtis indicated he would research information on intensive systems.

Objective: Continue to develop guidance for methods for PEC calculations.

4. Getting together a list of commercial and other labs or organizations that specialize in environmental work, especially toxicology work was discussed.

Objective: CVM said they are going to try to put together a source for resource laboratories for environmental studies. The source will not be comprehensive nor is it an endorsement of any laboratories. The source will only be a general representation of laboratories that have provided data and those obtained from other sources.

5. General Discussion items:

a. Eric Silberhorn said that we are probably depriving ourselves of useful toxicity data because our searches gather results from mostly American literature sources. CVM will look into ways of accessing larger worldwide databases. Eric said that nonpublished or self-published toxicity studies at, e.g., the state level are not that numerous and also may not be that useful for formal toxicity assessment if they are not conducted in laboratory water. There was also a discussion of possibly writing a letter to the editor of some prominent aquaculture journal requesting that

the readers submit unpublished studies of toxic endpoints for aquaculture drugs that they are aware of to the Forum.

b. It was suggested that specific drugs be listed, in order of priority or need, but the sponsor representative said that such a list may be delicate from the sponsors' standpoints, especially with regard to the overseas market. It was agreed not to include a list if such a letter would be sent out.

c. CVM is looking forward to putting our EA(s) on their website.

**ANALYTICAL METHODS VALIDATION**

Co-leaders: Jeff Meinertz & James Nitao
Participants:

At the meeting in Bozeman, the following 6-month plan and ultimate goal was developed: The goal was to develop a Science Report that would describe the level of method validation necessary for analytical methods supporting studies conducted to address issues in each technical section of the drug approval process. The initial step we decided upon to achieve this goal was to conduct an outreach exercise where we would (1) add to the group CVM reviewers associated with the human food safety, efficacy and target animal safety, and environmental safety technical sections and (2) add to the group a participant from the FWS, and in particular, someone from the Bozeman office. The next step would then be to post an e-mail to all participants formally describing the objectives of the group and outline an approach to achieve the objectives. Then we would convene a conference call to identify the core group of participants, clarify the objectives, discuss the approach, and develop another 6 month or 1 year plan.

**ANTIMICROBIAL RESISTANCE**

Co-leaders: Steve Yan & Christine Moffitt
Participants: Tom Bell, Joy Evered, Bill Gingerich, and Roz Schnick

The group discussed the general data requirements for microbial food safety evaluation under GFI#152, and it was emphasized that the focus microbial food safety assessment should be placed on index food-borne pathogens (such as *salmonella* and *campylobacter*) and some commensal bacteria (such as *E. coli* and enterococci) that may harbor and transfer resistant genetic elements to index food-borne pathogens. Although paper arguments based on literatures are welcomed for the qualitative risk assessment (under GFI#152), sometimes, published data are either lack of relevant information or not specifically tailored to conditions of aquaculture drug use. The group felt, sometimes, that limited data collections or monitoring would be more helpful in mitigating particular concerns associated with aquaculture drug applications. The group then briefly talked about how and what kind of studies can be done to fulfill the release assessment if data gaps exist. It is the intent of this group to gain a better understanding of the complete data and information requirements necessary to address the antimicrobial food and safety concerns and to be able to use this understanding to facilitate addressing such concerns for future aquaculture drug applications.

When addressing specific information requirements and data gaps for an expanded/extended claim of a compound currently approved and for an initial claim for a compound yet to be filed for approval, the group expressed a need to arrange a meeting between members of CVM's

Microbial Food Safety and the respective drug company sponsors to discuss the best methods to address CVM's concerns regarding microbial food safety data requirements. Ms. Roz Schnick will contact CVM's Microbial Food Safety Team and coordinate the meeting.